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|---|---|
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| ART UNIT | PAPER NUMBER |
| 1652 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/616,309 | RIEPING ET AL. | |
| | Examiner | Art Unit | |
| | Lindsay Odell | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12 March 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: result 4

## DETAILED ACTION

### *Application Status*

1. In response to the previous Office action, a written restriction requirement (mailed on March 7, 2005), Applicants filed a response received on April 5, 2005. Claims 1-33 are pending in this instant Office action.

### *Election*

2. Applicant's election with traverse of Group II, Claims 19-20 in the reply filed on April 5, 2005 is acknowledged. The traversal is on the grounds(s) that no undue burden would be placed on the Examiner to examine all the pending claims together. This is not found persuasive because the Groups of claims are distinct for the reasons previously cited, and the searches are not co-extensive because the groups are classified differently and the searches in textual databases are different; thus, the Groups of claims would be burdensome to be searched together.

The requirement is still deemed proper, and is, therefore, made FINAL. Examiner acknowledges the amendment filed April 5, 2005, which adds new claims 22-33, which belong in elected Group II. Thus, Group II encompasses claims 19-33.

### *Requirement for an Election of Species*

3. This application contains claims directed to the following 65 patentably distinct species of the claimed invention II: each of the microorganisms listed in claims 31 and 33 in which the

microorganism used additionally has enhancement or attenuation of a particular gene that is distinct from *rseB*.

The species of instant processes are patentably distinct, each from the other, because the microorganisms used in the processes have different structures. The searches required for the species are not co-extensive because inspection of the prior art for each species is different. It is, therefore, burdensome to search all of the claimed species together.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for claimed invention II for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently claims 19-30 and 32 are generic.

Applicant's provisional election of the species "the *thrABC* operon", which is readable upon claim 31, is acknowledged in order to expedite examination. The Examiner has extended examination to include the species "the *rseA* gene" listed in claim 31 because no prior art was found that anticipates the elected species "the *thrABC* operon".

Claims 1-33 are pending in the instant Office action. Claims 1-18 are withdrawn as non-elected inventions. Prosecution on the merits of claim 31 has been restricted to the species "the *thrABC* operon" and "the *rseA* gene". Claim 33 is drawn to non-elected species. Claims 19-31, including the species "the *thrABC* operon" and "the *rseA* gene", and 32 are examined herein.

***Priority***

4. The instant application is granted the benefit of priority for the U.S. provisional Application No. 60/395621 filed on July 15, 2002 as requested in the declaration and the first lines of the specification.

5. The instant application is granted the benefit of priority for the foreign application 102 31 115.3 filed in Germany on July 10, 2002 as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d) or (f), which papers have been placed of record in the file.

***Information Disclosure Statement***

6. The lists of related cases submitted on November 3, 2002, April 20, 2004 and July 6, 2004 have been received and placed in the file.

7. The information disclosure statement filed on March 12, 2004 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

***Compliance with Sequence Rules***

8. The sequence listing, filed in computer readable form (CRF) and paper copy on July 10, 2003, and the statement regarding the sameness of the paper copy and CRF, filed on July 10, 2003, have been received and entered.

***Objections to the Specification***

9. The specification is objected to because the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Enterobacteriaceae strains over-expressing the *rseB* gene for the fermentative preparation of L-threonine---.

10. The disclosure is objected to because of the following informalities. The phrase "and in which the nucleotide sequence which codes for the rseB gene is enhanced" in the first sentence on page 4 is confusing because nucleotide sequences do not encode genes, which are themselves, composed of nucleotides. The Examiner suggests using the language ---and in which expression of the *rseB* gene is enhanced---. Appropriate correction is required.

***Claims Objections***

11. Claim 20 is objected to because of improper antecedent basis. The term "A microorganism according to Claim 19" does not properly refer to the recombinant microorganism of claim 19. Examiner suggests using the language: ---The recombinant microorganism of Claim 19---. Appropriate correction is required.

12. Claim 21 is objected to because of improper antecedent basis. The phrase "The microorganism of Claim 19, which is a recombinant microorganism which is generated by transformation" is awkward and does not properly refer to the recombinant microorganism of

Claim 19. Examiner suggest using the language: ---The recombinant microorganism of Claim 19, which is generated by transformation---

13. Claim 24 is objected to because of the following informalities. The phrase "incorporation of a vector which replicates extrachromosomally into said microorganism" is confusing because the vector does not replicate into said microorganism; it is incorporated into said microorganism. The Examiner suggests placing commas before and after the phrase "which replicates extrachromosomally". Appropriate correction is required.

14. Claim 25 is objected to because of the following informalities. The claim includes to parts: c) and d); however, there are no parts a) or b), which is confusing. The Examiner suggests changing the lettering such that parts c) and d) become a) and b). Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 19-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**the** *rseB* gene" (emphasis added) as it appears in claims 19, 25 and 28 is unclear as to the metes and bounds it imparts on the claimed subject matter. Does **the** *rseB* gene that is over-expressed need to be the gene from the organism it is being over-expressed in?

Or can **the** *rseB* gene that is over-expressed be *any rseB* gene? For example, does the claim encompass *Erwinia papayae* in which the *Escherichia coli rseB* gene is over-expressed, or only *Erwinia papayae* in which the *Erwinia rseB* gene is over-expressed. Examiner suggest using the language ---an *rseB* gene---.

In addition, the name "*rseB* gene" is insufficient to describe the genus of *rseB* genes because a family of *rseB* genes is not well-known in the art. An explicit definition for "*rseB* gene" is not disclosed in the specification. Is an *rseB* gene any gene that is structurally similar to the *E. coli rseB* gene disclosed by Applicant? Alternatively, is an *rseB* gene any gene that shares a similar function to the function disclosed for *E. coli rseB*? In addition, how similar in structure or function must a gene be to be considered an *rseB* gene? Clarification on all of the above points is required.

16. Claims 19-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "present in over-expressed form" as it appears in claim 19, is confusing because the *rseB* gene, itself, looks the same whether or not it is over-expressed, i.e. an expression cassette upstream of the *rseB* gene does not change the form of the *rseB* gene. Does Applicant mean to claim microorganisms in which the *rseB* gene is present in a particular construct, i.e. in which a strong exogenous promoter is upstream of the *rseB* gene? Or, does Applicant mean to claim microorganisms in which the *rseB* gene is over-expressed? Clarification is required.

17. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "promoter and regulation region or the ribosome-binding site" (emphasis added) is confusing. A promoter is a type of regulation region, so it is unclear what it means to have both a promoter and a regulation region. It is unclear if only the promoter upstream the *rseB* gene needs to be mutated or if both the promoter and another regulation region needs to be mutated. Clarification is required.

18. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "the activity . . . of the *rseB* gene product" (emphasis added) is unclear to the metes and bounds it imparts on the claimed subject matter. Two activities are disclosed on page 8 of the specification for the *rseB* gene product: 1) to improve production of L-threonine and 2) to down-regulate sigmaE activity. It is unclear which activity is **the** activity of the *rseB* gene product. Clarification is required.

19. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "gene(s) in which the biosynthesis pathway . . . is additionally enhanced" is confusing because it indicates that genes, which are composed of nucleic acids and which encode proteins, contain biosynthesis pathways. Does Applicant mean to claim microorganisms which contain one or more genes and in which the biosynthesis pathway is

additionally enhanced? Or, does Application mean to claim genes which are in the biosynthesis pathway? If Applicant means to claim the latter, it is additionally unclear what the metes and bounds of are "genes in the biosynthesis pathway of the desired L-amino acid". Metabolic pathways *Enterobacteriaceae* are complex and overlapping with far-reaching effects that might produce or reduce amino acid formation. A clear definition of which enzymes are involved is required, either from the specification or the art, for all the L-amino acids intended to be encompassed by the scope of the claims. Clarification of all of the above points is required.

20. Claims 30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**desired** L-amino acid" (emphasis added) as it appears in the claims is unclear as to the metes and bounds it imparts on the claimed subject matter. It is unclear how to anticipate what L-amino acid Applicant "desires" to claim. Does Applicant mean to claim a particular amino acid or does Applicant mean to claim any L-amino acid? Clarification is required.

21. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of "metabolic pathway, which reduces the formation of the desired L-amino acid" is unclear. Metabolic pathways in *Enterobacteriaceae* are complex and overlapping with far-reaching effects that might produce or reduce amino acid formation. A clear definition of which enzymes are involved is required, either from the specification or the

art, for all the L-amino acids intended to be encompassed by the scope of the claims. Clarification is required.

22. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear exactly which genes must be enhanced in the instant claims and by what means. The *thrABC* and *rseA* gene names are known for *E. coli;* however, the claims are drawn to any *Enterobacteriaceae.* If the genes for aspartate kinase, homoserine dehydrognase, homoserine kinase and threonine synthase, for example, are not collectively named *thrABC* in all *Enterobacteriaceae*, what operon is to be enhanced? It is unclear whether Applicant means to claim a genus of genes limited by their name or name abbreviation or limited by the enzyme or protein encoded by those genes. Moreover, if *E. coli* is the microorganism, must the *E. coli thrABC* operon be used in the methods to enhance the *thrABC* operon or can *any* aspartate kinase, homoserine dehydrognase, homoserine kinase and threonine synthase operon (from any organism) enhance the *thrABC* operon in the method? The word "the" before the gene names indicates that Applicant means to claim specific genes, however it is unclear which specific genes Applicant means to claim. Clarification on all these points is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 19-32 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to recombinant microorganisms of the *Enterobacteriaceae* family in which the *rseB* gene or *rseB* gene variants are present in over-expressed form. While the function and structure of a species of the instant genera of *rseB* genes are disclosed in the specification, a representative number of species and the common functional or structural characteristics of species that describe said genera are not identified.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

On pages 8-9 of the instant specification, an *rseB* gene is disclosed that functions to encode a protein that regulates sigmaE activity (or to increase L-threonine production) and has a structure described by SEQ ID NO: 3 (*E. coli rseB*). Applicants have adequately described *rseB* genes containing structural features of the genus relating to *E. coli rseB* (SEQ ID NO: 3) that are over-expressed; however, a functional limitation for *rseB* genes or *rseB* gene variants is lacking and the common structural characteristics of the species in the instant genera of *rseB* genes that correlate to such a functional limitation are lacking. In view of the prior art, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to the instant genus of microorganisms are not adequately described.

24. Claim 25 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to recombinant microorganism of the *Enterobacteriaceae* family wherein over-expression of the *rseB* gene or gene variant is achieved by mutating the promoter upstream of the *rseB* gene. While the function of the instant bacteria promoter is disclosed in the specification, sufficient structure for the genus of instant promoters and function that correlates to that structure is lacking.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject

matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, over-expression of the *E. coli rseB* gene in the vector pTrc99a, which places the *rseB* gene under the control of an **exogenous** promoter, is described; however, the structure of promoters and regulation regions on the chromosome of *Enterobacteriaceae* bacteria are not disclosed. While generic promoters that increase gene expression are known in the art, a particular, endogenous promoter and regulation region for the *rseB* gene, or gene variants, is not described. Without description of the endogenous promoters or regulation regions for the *rseB* gene or gene variants, an endogenous promoter or regulation region that has been specifically altered (mutated) to increase expression of said protein also lacks adequate written description. Although *rseB* genes that are over-expressed due to insertion of an exogenous promoter upstream of the genes are adequately described, a single species of *Enterobacteriaceae* with mutated endogenous promoters and regulation regions that cause over-expression of the *rseB* gene are not described. The structure of representative number promoters upstream of the *rseB* gene or gene variants, as well as the common characteristics that define the

structure of the genus of promoters or gene variants, are also not adequately described. One of skill in the art would be unable to predict the structure of members of this genus by virtue of the instant disclosure. Therefore, claims drawn to the instant genus of *Enterobacteriaceae* with mutated promoters and regulation regions, is not adequately described.

25. Claim 27 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to recombinant microorganisms of the *Enterobacteriaceae* family in which the *E. coli rseB* gene or *rseB* gene variants are present in over-expressed form, and which have at least one additional metabolite or antimetabolite resistance mutation. Neither the function or structure of a single species of the instant genera of *Enterobacteriaceae* having an additional metabolite or antimetabolite resistance mutation are disclosed in the specification.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the

common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

One species of *Enterobacteriaceae* with an over-expressed *rseB* gene is disclosed in the specification (see above). However, neither the structure or function of a single species of the instant *Enterobacteriaceae* with additional metabolite or anti-metabolite resistance mutations are described. While some metabolite and anti-metabolite resistance mutations are known in the art, the structure of a representative number of species of the instant resistance mutations, and the common structural and functional characteristics that define the instant genus of resistance mutations, are lacking. In view of the prior art, one of skill in the art would be unable to predict the structure of members of this genus by virtue of the instant disclosure. Therefore, claims drawn to the instant genus of *Enterobacteriaceae* are not adequately described.

26. Claims 30 and 32 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to recombinant microorganisms of the *Enterobacteriaceae* family in which genes in an L-amino acid biosynthesis pathway are over-expressed (claim 30) or which have at least one metabolic pathway that reduces the formation of the desired L-amino acid attenuated (claim 32). The

structure and function of genes and enzymes involved in the aforementioned pathways is not disclosed in the specification.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

On pages 14-19 of the instant specification, some genes in the biosynthesis pathway of L-threonine are disclosed. The structural and functional features of some genes in the biosynthesis pathway for L-amino acids and metabolic pathways that reduce the formation of amino acids in *Enterobacteriaceae* are known. However, a representative number of species of each gene and enzyme in said pathways, and the common structural characteristics of the species in the instant genera that correlate to a functional limitation are lacking. In view of the prior art, one of skill in the art would be unable to predict the structure of all the other members of these genera by virtue

of the instant disclosure. Therefore, claims drawn to the instant genera of microorganisms are not adequately described.

27. Claim 31 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to recombinant microorganism of the *Enterobacteriaceae* family in which the *rseB* gene is over-expressed and an additional gene is over-expressed that is claimed solely by name and without any structural limitations; the specific gene, *rseA* is claimed as follows: coding for a membrane protein with anti-sigmaE activity.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

Unlike genes such as *pyc* encoding pyruvate carboxylase, the instant gene encodes a protein that does not have a well-known structure associated with it in the art. The instant specification describes one example of each on page 17. In the claim, the *rseA* gene is only described according to the functional characteristics of the protein that it encodes; no structural relationship is described or used. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, the instant claim, drawn to microorganisms over-expressing the *rseA* gene, is also not adequately described.

28. Claims 19-32 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for *Enterobacteriaceae* in which the *E. coli rseB* gene is over-expressed by certain means, does not reasonably provide enablement for the genera of *Enterobacteriaceae* in which any *rseB* gene or *rseB* gene variants are over-expressed. To make all the *Enterobacteriaceae* included in the scope of these claims would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The specification contains one working example of an *Enterobacteriaceae* microorganism in which the *rseB* gene is present in over-expressed form: an *E. coli* bacterium transformed with a vector containing *E. coli rseB* (described by SEQ ID NO: 3) under control of an exogenous promoter (pages 24-25). This organism is used to improve the production of L-threonine by approximately 64% compared to untransformed *E. coli* (pages 25-26).

Applicants, however, present no guidance or working examples of the use of *Enterobacteriaceae* containing any *rseB* gene or *rseB* gene variant. The nature of the invention is such that the DNA encodes a functional protein, which functions to regulate sigmaE by interacting with the C-terminal domain of the *rseA* protein; and with a deviation from the known sequence, the predictability of functionality becomes extremely low. The predictability of making isolated nucleotides that encode polypeptides related to *E. coli rseB* (SEQ ID NO: 3) which also maintain the function of an *rseB* gene product can be increased by comparing the sequences of a genus of known *rseB* proteins to SEQ ID NO:3 and identifying important/conserved residues. However, no examples of other *rseB* genes are indicated in the

specification, and the state of the prior art is such that only a couple of other *rseB* genes are known; thus, a comparison of a sufficient number of sequences of *rseB* genes to the disclosed *rseB* gene from *E. coli* cannot be performed. While the art describes methods for finding *rseB* genes and *rseB* gene variants, these methods do not enable one of skill in the art to make all, or a relevant portion of, the molecules within the scope of the claims. The ability to find an *rseB* gene or *rseB* gene variant within the scope of the instant claims is not equivalent to the ability to make a mutant strain as required by the statute (i.e., "make and use").

The breadth of the claims and the unpredictability of the art render the instant claims not enabled to the full extent of their scope without undue experimentation.

29. Claims 19-32 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *Escherichia* strains in which over-expression is achieved by inserting a known strong promoter upstream of the *rseB* gene, does not reasonably provide enablement for the genus of *Enterobacteriaceae* that are over-expressed by any means. The specification does not enable a person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The ability to make all *Enterobacteriaceae* bacteria included in the scope of these claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988), are stated above. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The art teaches how to select *Enterobacteriaceae* bacteria that have an increased production of L-amino acids, how to mutagenize chromosomal DNA and how to characterize the mutations in the DNA. However, neither the specification nor the art contain any examples of how to specifically change endogenous *Enterobacteriaceae* chromosomal promoter and regulation regions upstream of the *rseB* gene such that the expression of said gene is increased. The art provides enablement for inserting a known promoter in the chromosomal DNA to upregulate the expression of *E. coli rseB* gene; however, neither the specification nor the art enable making specific changes to promoters and regulation regions for the *rseB* gene (as specifically required by claim 25). The art and specification lack a detailed description of the structure of the instant endogenous promoter and regulation regions, and they lack any guidance on how to alter such sequences such that *rseB* expression is increased; therefore, to make the instant *Enterobacteriaceae* with mutated promoters and regulation regions would be unpredictable.

While the prior art combined with the instant specification describe means for identifying *Escherichia* bacteria that have increased *rseB* expression due to alteration in the promoter and regulation regions for *rseB*, these methods do not enable one of skill in the art to make all, or a relevant portion of, the *Enterobacteriaceae* within the scope of the claims. The ability to find an *Enterobacteriaceae* with mutated promoter and regulation regions upstream of the *rseB* gene that increase *rseB* expression, is not equivalent to the ability to make *Enterobacteriaceae* with mutated promoter and regulation regions upstream of the *rseB* gene, as required by the statute (i.e., "make and use"). No description in the specification or the art provides the structure of the expression regulation sequence and the particular nucleic acid residues that are important within

the sequence such that the activity of said protein, and L-amino acid production are enhanced. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

30. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, enablement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims is drawn to *Enterobacteriaceae* in which the *rseB* gene is over-expressed and which have metabolite or antimetabolite resistance mutations. To make the *Enterobacteriaceae* encompassed by the scope of the instant claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Applicants present no guidance or working examples of the use of *Enterobacteriaceae* containing any *rseB* gene or *rseB* gene variant which have additional metabolite or anti-metabolite resistance mutations. While the prior art combined with the instant specification describe means for identifying *Enterobacteriaceae* that have metabolite or anti-metabolite resistance mutations, these methods do not enable one of skill in the art to make all, or a relevant portion of, the *Enterobacteriaceae* within the scope of the claims. The ability to find *Enterobacteriaceae* with a an additional metabolite or antimetabolite resistance mutations is not equivalent to the ability to make *Enterobacteriaceae* with additional metabolite or antimetabolite

resistance as required by the statute (i.e., "make and use"). Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members.

31. Claim 28 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *Enterobactericeae* strains in which L-threonine production is increased (as shown in Table 1) by the over-expression of the *rseB* gene, does not reasonably provide enablement for the genus of *Enterobacteriaceae*, wherein the activity or concentration of the *rseB* gene is increased from 10-100%. The specification does not enable a person skilled in the art to which the invention pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The ability to make all *Enterobacteriaceae* bacteria included in the scope of these claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988), are stated above. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

On pages 24-25, the specification discloses an *E. coli* bacterium transformed with the *E. coli rseB* gene described on pages 24-25 (see previous 112, 1st paragraph rejection) that increases L-threonine production by approximately 77%. An increase in L-threonine production can be as an increase in *rseB* product activity. Thus, the specification contains one working example of an *Enterobacteriaceae* microorganism in which the activity of the *rseB* gene product is increased by least 10%. Applicants, however, present no working examples of *Enterobacteriaceae* in which L-threonine production is increased by more than 76%, or in which

any other type of measurable *rseB* gene product activity is increased by at least 10%. The state of the prior art is such that another activity for the *rseB* gene product is known (regulating anti-sigma E activity), but measured increases of this specific activity or L-threonine producing activity as a result of *rseB* over-expression in the range of 76-100% have not been measured. The nature of the invention is such that increasing the activity of the *rseB* gene product as much as 100% can be difficult due to protein aggregation, insolubility and other metabolic effects that occur when a protein is over-expressed. Thus, the predictability of making *Enterobacteriaceae* that have an increase of over 76% of L-threonine production,, or another *rseB* gene product activity that is due to *rseB* over-expression, is low. The breadth of the claims and the unpredictability of the art render the instant claims not enabled to the full extent of their scope without undue experimentation.

32. Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for *Enterobacteriaceae* in which the *E. coli rseA* gene and *E. coli thrABC* operon are enhanced by increased expression due to introduction of an exogenous promoter, does not reasonably provide enablement for the genera of *Enterobacteriaceae* in which any additional gene in an L-amino acid biosynthesis pathway is over-expressed or enhanced in any way (claim 30), in which any *thrABC* operon or any *rseA* gene is over-expressed or enhanced in any way (claim 31), or in which any gene in an L-amino acid biosynthesis pathway is attenuated by any means. To make all the *Enterobacteriaceae* included in the scope of these claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized In re

Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988), are stated above. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The structure of the *E. coli thrABC* operon and the *E. coli rseA* gene are known in the art; thus, one of skill in the art would be enabled to achieve over-expression of these genes by inserting of an endogenous promoter upstream of them. However, on pages 4 and 12-13, the specification describes enhancement as including increasing gene copy number, using potent promoters, mutating the promoter upstream of the gene, increasing enzyme activity by preventing degradation of the enzyme, prolonging m-RNA lifetime and changing the composition of the media. Neither the art nor specification provide guidance on how to achieve increasing enzyme activity by preventing degradation of the enzyme, prolonging m-RNA lifetime and changing the composition of the media for the instant *rseA* and *thrABC* genes or for any other genes. The art and specification lack a detailed description of the structures of the instant endogenous promoters for the instant *rseA* and *thrABC* genes or any other genes, and they lack any guidance on how to alter such sequences such that these genes or any particular gene's expression is increased. To make the instant *Enterobacteriaceae* with mutated promoters to enhance expression would, be unpredictable. Likewise, to make the instant *Enterobacteriaceae* with stabilized m-RNA for the breadth of genes encompassed by the claims would be unpredictable since to guidance is given on in the art or specification on how to achieve such over-expression.

In addition, on pages 20-21, the specification describes attenuation as including using weak promoters or alleles encoding enzymes with lower activity. The art provides enablement for deleting genes of L-amino acid biosynthesis pathways of known structure to attenuate their

activity; however, neither the specification nor the art enable using alleles that code for a corresponding enzyme having a lower activity or weak promoters to attenuate a genes. The specification contains no working examples of *Enterobacteriaceae* in which *rseB* is over-expressed that have any additional genes attenuated by any of the aforementioned measures. The art and specification lack a detailed description of the structures of the breadth of the instant genes to be attenuated, and they lack any guidance on how to specifically alter such genes so that it's expression is attenuated. Likewise, the art and specification lack a detailed description of alleles that code for a corresponding enzyme having a lower activity. Therefore, to make the instant *Enterobacteriaceae* with alleles that code for a corresponding enzyme having a lower activity would be unpredictable.

While the prior art combined with the instant specification describe means for identifying *Escherichia* bacteria that have increased gene expression due to alteration in the promoter or are attenuated by mutations that weakens a gene's promoter, these methods do not enable one of skill in the art to make all, or a relevant portion of, the *Enterobacteriaceae* within the scope of the claims. The ability to find an *Enterobacteriaceae* with mutated promoter upstream of a particular gene that increases or attenuates its expression, is not equivalent to the ability to make *Enterobacteriaceae* with mutated promoter the gene that attenuates or increases its expression, as required by the statute (i.e., "make and use").

The breadth of the claims and the unpredictability of the art render the instant claims not enabled to the full extent of their scope without undue experimentation.

***Claim Rejections - 35 USC § 102***

33. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

34. Claims 19, 21-22, 24-26 and 29 are rejected under 35 U.S.C. § 102(b) as being anticipated by De Las Penas *et al.* (see IDS). The instant claims are drawn to recombinant *Enterobacteriaceae* in which the *rseB* gene is over-expressed (claim 19), that are optionally generated by transformation with a vector containing an *rseB* gene (claim 21), or wherein the number of *rseB* gene copies is optionally increased by at least one (claim 22), or wherein the number of *rseB* gene copies is increased by at least one and said increase is achieved by a vector which replicates extrachromosomally (claim 24), or wherein over-expression is achieved by incorporation of an expression cassette upstream of the *rseB* gene (claim 25), or which has optionally been transformed with an *rseB* gene under control of a promoter (claim 26), or which is optionally *Escherichia* (claim 29).

De Las Penas *et al.* teach cloning the *E. coli rseB* gene into the pET24 vector using the restriction sites *Eco*RI and *Hind*III, transformation of said vector into *E. coli* BL21, and over-expression of the *rseB* gene using said transformed *E. coli* (Figure 5.a., page 381, columns 1 and

2). The pET24 vector is an expression vector that contains a T7 promoter and a *lac* operator upstream of the multiple cloning region (where the *E. coli rseB* gene was cloned by De Las Penas) and an f1 origin of replication (see attached vector map). The f1 origin of replication allows for multiple copies of the instant vector to be made in a single bacterium extrachromosomally. The location of the multiple cloning site places the *rseB* gene under the control of the T7 promoter. In the broadest reasonable terms, the T7 promoter and *lac* operator, which are upstream of the *rseB* gene, constitute an expression cassette. Thus, the microorganism taught by De Las Penas *et al.* embodies every aspect of claims 19, 21-22, 24-26 and 29.

35. Claim 20 is rejected under 35 U.S.C. § 102(b) as being anticipated by De Las Penas *et al.* (see IDS) as evidenced by PGPUBS 20050032178. The instant claims are drawn to recombinant *Enterobacteriaceae* in which the *rseB* gene is over-expressed and which produce L-threonine.

De Las Penas *et al.* teach cloning the *E. coli rseB* gene into the pET24 expression vector, transformation of said vector into *E. coli* BL21 and over-expression of the *rseB* gene using said transformed *E. coli*, as previously described. *Escherichia coli* produce L-threonine, as evidenced by PGPUBS 20050032178, which discloses that "It is known that L-amino acids are prepared by fermentation of strains of *Enterobacteriaceae*, in particular *Escherichia coli* (*E. coli*) and *Serratia marcescens*." (see page 2). Thus, the bacterium taught by De Las Penas *et al.* embodies every aspect of claim 20 because in is an *E. coli* bacterium.

36. Claims 19, 21-22, 29 and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Missiakas *et al.* (see IDS). The instant claim is drawn to a recombinant *Enterobacteriaceae*

bacterium in which the *rseB* gene is over-expressed (claim 19), optionally by transformation with a vector containing an *rseB* gene (claim 21), optionally wherein the number of *rseB* gene copies is increased by at least one (claim 22), optionally wherein the microorganism is in the genera *Escherichia* (claim 29), or optionally wherein the *rseA* gene is additionally over-expressed (claim 31).

Missiakas *et al.* teach the over-expression of the *rseB* and *rseA* genes together on a plasmid in *E. coli* (see Figure 5 and page 367, column 2). Thus, Missiakas *et al.* anticipate claims 19, 21-22, 29 and 31.

37. Claims 19-22, 24, 26 and 29 are rejected under 35 U.S.C. § 102(e) as being anticipated by Drmanac *et al.* (WIPO Pub WO 200175067 A2, see ~~attached~~ PTO-892 IE) as evidenced by PGPUBS 20050032178. The instant claims are drawn to recombinant *Enterobacteriaceae* in which the *rseB* gene is over-expressed (claim 19), that optionally produce L-threonine (claim 20), or which are optionally generated by transformation with a vector containing an *rseB* gene (claim 21), or wherein the number of *rseB* gene copies is optionally increased by at least one (claim 22), or which has optionally been transformed with an *rseB* gene under control of a promoter (claim 26), or which are optionally *Escherichia* (claim 29).

Drmanac *et al.* teach *Escherichia coli* transformed with SEQ ID NO: 17871, and open reading frames (ORF's), thereof, in an expression vector containing a promoter, and expression of said SEQ ID, or ORF's, thereof, (page 18, line 29; page 19, lines 23-25; page 20, line 3; page 25, lines 20-22). SEQ ID NO: 17871 contains a sequence that is 99.8% identical to the *E. coli* *rseB* gene disclosed by Applicant (SEQ ID NO: 3); thus, it is considered to contain an *rseB* gene

or *rseB* gene variant (see sequence alignment, ~~PTO-892~~ attached 20). Lastly, *Escherichia coli* produce L-threonine, as evidenced by PGPUBS 20050032178, which discloses that "It is known that L-amino acids are prepared by fermentation of strains of *Enterobacteriaceae*, in particular *Escherichia coli* (*E. coli*) and *Serratia marcescens*." (see page 2). Therefore, the *Escherichia coli* taught by Drmanac *et al.* embody every aspect of claims 19-22, 24, 26 and 29.

***Other Art for Comment***

The following are cited to complete the record:

a) Parkhill *et al.* (see PTO-892) teach *Salmonella enterica rseB*; however they do not teach it in over-expressed form.

b) Perna *et al.* (see PTO-892) teach *E. coli rseB*; however, they do not teach it in over-expressed form.

***Conclusion***

38. Claims 19-32 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lindsay Odell whose telephone number is 571-272-3445. The examiner can normally be reached on M-F, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lindsay Odell, Ph.D.
May 27, 2005

KATHLEEN KERR, PH.D
PRIMARY EXAMINER